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(54) Title: ENANTIOSELECTIVE PREPARATION OF PHARMACEUTICALLY ACTIVE SULFOXIDES BY BIOOXIDATION

(57) Abstract

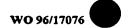
A compound of formula (II) is prepared either as a single enantiomer or in an enantiomerically enriched form, wherein Het1 is (a) or (b) and Het2 is (c) or (d) and X is (e) or (f) wherein N in the benzimidazole moiety means that one of the carbon atoms substituted by R6-R9 optionally may be exchanged for an unsubstituted nitrogen atom; R1, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl, phenylalkoxy; R4 and R4 are the same or different and selected from hydrogen, alkyl, aralkyl; R5 is hydrogen, halogen, trifluoromethyl, alkyl, alkoxy; R6-R9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl or adjacent groups R6-R9 may complete together with the carbon atoms to which they are attached optionally substitued ring structures; R10 is hydrogen or alkoxycarbonyloxymethyl; R11 is hydrogen or forms an alkylene chain together with R3; R12 and R13 are the same or different and selected from hydrogen, halogen or alkyl, by a method comprising stereoselective biooxidation of the pro-chiral sulfide counterpart compound.

$$R_1$$
 R_2 R_3 (a)

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Enantioselective preparation of pharmaceutically active sulfoxides by biooxidation

The present invention relates to a method of preparing compounds as defined below, either as a single enantiomer or in an enantiomerically enriched form, by biooxidation of their sulphide equivalents.

Background to the Invention

- 10 The racemic form of the compounds prepared by the method of the present invention are known compounds. Some of the compounds are also known in single enantiomeric form. The compounds are active H*K*ATPase inhibitors and they, including their pharmaceutically acceptable salts, are effective acid secretion inhibitors, and known for use as antiulcer agents. The compounds, which include the known compounds omeprazole (compound of formula (IIa) below), lansoprazole (compound of formula (IIc) below) and pantoprazole (compound of formula (IIb) below), are known for example from European Patent Specifications EP 5129 and 124495, EP 174726 and EP 166287.
- These compounds, being sulfoxides, have an asymmetric centre in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.
- The separation of enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19. Also the separation of enantiomers of compounds, including omeprazole and pantoprazole, is described in German Patent Specification DE 4035455.

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Recently there has been a great deal of literature published relating to the synthesis of optically active compounds using biocatalysts. The majority of this work has been aimed at finding routes to single enantiomer forms of pharmaceuticals. The reactions receiving most attention have been those involved in the preparation of esters, acids and alcohols due to the general utility of these functionalities in synthesis and also because the biocatalysts are readily available.

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Studies on the synthesis of optically active sulfoxides are relatively rare partly due to the small number of pharmaceuticals containing sulfoxide groups and partly due to the fact that enzymes that react with the sulphur centre are not available commercially. The synthesis of optically active sulfoxides has been described in Holland, H.L. (1988) Chem. Rev. <u>88</u>, 473–483 and Phillips, R.S. and Sheldon W.M., Enzyme Microb. Technol., 1981, Vol. 3, January, 9-18.

15 Description of the Invention

According to the present invention there is provided a method of preparing a compound of formula (II) either as a single enantiomer or in an enantiomerically enriched form:

20

wherein

Het
$$_1$$
 is R_1 or R_4

25 and

or N

and

X is
$$-CH$$
 or R_{12}

wherein:

5

20

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_s - R_s optionally may be exchanged for an unsubstituted nitrogen atom;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl, phenylalkoxy;

 R_4 and R_r are the same or different and selected from hydrogen, alkyl, aralkyl;

15 R_s is hydrogen, halogen, trifluoromethyl, alkyl, alkoxy;

 R_s - R_s are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl or adjacent groups R_s - R_s may complete together with the carbon atoms to which they are attached optionally substituted ring structures;

R₁₀ is hydrogen or alkoxycarbonyloxymethyl;

R₁₁ is hydrogen or forms an alkylene chain together with R₂;

R₁₂ and R₁₃ are the same or different and selected from hydrogen, halogen or alkyl, which method comprises stereoselective biooxidation of the pro-chiral sulfide counterpart compound.

The compounds of formula (II) are active H'K'ATPase inhibitors. By the method of the invention these compounds, which are sulfoxides, are obtained in single enantiomer form or such that one enantiomeric form is present in excess leading to an optically active product, by stereoselective biooxidation of the pro-chiral starting sulfide counterpart compound.

In the above definitions alkyl groups or moieties may be branched or straight chained or comprise cyclic alkyl groups, for example cycloalkylalkyl.

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10

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Preferably:

$$R_1$$
 R_3

and

20

and

(wherein R_1 , R_2 , R_3 , R_6 to R_5 , R_{10} and R_{11} are as defined above).

Most preferably the compounds of formula (II) are compounds of the formula (IIa) to (IIe):

$$H_3C$$
 CH_3
 CH_3
 OCH_3
 OCH_3

10

5 An example of a compound of formula (II) wherein R_{10} is alkoxycarbonyloxymethyl is

The starting pro-chiral sulfides used in the method of the present invention are of the formula:

$$Het_1$$
— $X-S-Het_2$ (I)

wherein Het₁, X and Het₂ are as defined above.

In order to obtain each of the above compounds (IIa)-(IIf), the following starting compounds of formula (Ia) to (If), respectively will be required:

5

10

$$H_3C$$
 CH_3
 CH_3
 CH_3
 CH_3
 CH_3

The compounds prepared by the method of the invention possess a stereogenic (asymmetric) centre which is the sulfur atom which forms the sulfoxide group between the Het,-X-moiety and the Het,-moiety.

The stereoselective biooxidation according to the present invention may be carried out using a microorganism or an enzyme system derivable therefrom. Suitable microorganisms may be selected from alkane oxidisers including <u>Arthrobacter petroleophagus</u>, <u>Brevibacterium paraffinolyticum</u>, and <u>Acinetobacter</u> species, alkene oxidisers such as <u>Mycobacterium</u> species, and a variety of fungal species particularly <u>Penicillium</u> species (<u>Penicillium frequentans</u>).

15

According to one embodiment of the invention the method comprises contacting the pro-chiral sulfide counterpart compound with a microorganism which is

Penicillium frequentans

Rhizopus stolonifer

Cunninghamella elegans

Ustilago maydis

5 Arthrobacter petroleophagus

Brevibacterium paraffinolyticum

Acinetobacter sp.

Mycobacterium sp.

or Aspergillus niger

10 Preferably the microorganism is:

Penicillium frequentans BPFC 386, 585, 623, 733

Rhizopus stolonifer BPFC 1581

Ustilago maydis BPFC 1198, 6333

Arthrobacter petroleophagus ATCC 21494

15 <u>Brevibacterium paraffinolyticum</u> ATCC 21195

Actinetobacter sp. NCIMB 9871

Mycobacterium sp. BPCC 1174, 1178, 1179, 1186, 1187

- or Aspergillus niger BPFC 32
- The microorganisms may be grown on suitable medium containing an appropriate carbon source such as octane, ethene, cyclohexanone or glucose for example.

The compounds of formula (II) are generally acid labile and thus the use of acid conditions is to be avoided. Generally the method according to the invention may be carried out at a pH of 7.6 to 8, suitably about 7.6, and at temperature of 25-35°C, suitably about 28°C.

The present invention will now be illustrated with reference to the Examples.



EXAMPLE 1

The following microorganisms were screened for sulfoxidation activity against compounds of formula (Ia):

5

Penicillium frequentans BPFC 386

Penicillium frequentans BPFC 585

Penicillium frequentans BPFC 623

Penicillium frequentans BPFC 733

10 Rhizopus stolonifer BPFC 1581

Ustilago maydis BPFC 1198

<u>Ustilago maydis</u> BPFC 6333

Arthrobacter petroleophagus ATCC 21494

Brevibacterium paraffinolyticum ATCC 21195

15 Acinetobacter sp NCIMB 9871

Mycobacterium sp BPCC 1174

Mycobacterium sp BPCC 1178

Mycobacterium sp BPCC 1179

Mycobacterium sp BPCC 1186

20 Mycobacterium sp BPCC 1187

Growth Conditions

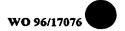
The growth conditions for the above microorganisms were as follows. The following fungi:

Penicillium frequentans BPFC 386

Penicillium frequentans BPFC 585

Penicillium frequentans BPFC 623

30 Penicillium frequentans BPFC 733



Rhizopus stolonifer BPFC 1581 Ustilago maydis BPFC 1198 Ustilago maydis BPFC 6333

were grown in 200 ml of sterile liquid medium (I) with the composition of (per litre) K,HPO, (1.9g), NaH,PO, 2H,O (2.02g), ammonium sulfate (1.8g), magnesium sulfate (0.2g), ferric chloride (0.97 mg), and trace elements solution (1 ml) pH 7.2. The composition of the trace elements solution used was as follows (in g/l):

10	CuSO, . 5H,0	0.02
	MnS0. 4H,0	0.1
	ZnS0, . 7H,0	0.1
	CaC0,	1.8

15 The above medium was supplemented with 0.2% w/v yeast extract and 2.2% w/v glucose. The medium contained in 1L baffled flasks was inoculated either by adding a suspension of spores in sterile distilled water or by the addition of a plug of agar containing the fungi from a Sabouraud Dextrose plate. Fungi were grown at 28°C on a rotary shaker at 150 rpm for 48 hours. With the exception of <u>Ustilago maydis</u>, the fungal biomass obtained from liquid culture was harvested by filtration on a Whatman Grade 113 filter paper and washed on the filter with 50 mM sodium phosphate buffer, pH7.6. <u>Ustilago maydis</u> was harvested by centrifuging for 20 minutes at 8,000 rpm and 4°C. The biomass was washed by resuspending in 50 mM sodium phosphate buffer, pH 7.6 and centrifuging as above.

25

The bacteria were grown with the sources of carbon shown in Table 1:



TABLE 1

Microorganism	Carbon Source
Arthrobacter petroleophagus ATCC 21494	Octane
Brevibacterium paraffinolyticum ATCC 21195	Octane
Acinetobacter sp NCIMB 9871	Cyclohexanone
Mycobacterium sp BPCC 1174, 1178, 1179, 1186, 1187	Ethene

The growth of <u>Acinetobacter</u> sp. NCIMB 9871 on cyclohexanone was performed in 100 ml of liquid medium (I) in a 500 ml baffled flask containing a centre well.

Cyclohexanone was placed in the centre well. The microorganism was grown at 28°C on a rotary shaker at 150 rpm for 24-48 hours.

Growth of Arthrobacter petroleophagus ATCC 21494 and Brevibacterium

10 paraffinolyticum ATCC 21195 on octane was performed in 200 ml of liquid medium

(I) containing 0.2% w/v yeast extract in a 1 L baffled flask. Octane (1ml) was added directly to the medium without sterilization. The above microorganisms were grown at 28°C on a rotary shaker at 150 rpm for 24-48 hours.

- Mycobacterium sp BPCC 1174, 1178, 1179, 1186 and 1187 were grown in 500 ml liquid medium (I) in a 2L non-baffled flask fitted with a rubber bung. The flask was partially evacuated and then charged with ethene. Growth was conducted at 28°C on a rotary shaker at 150 rpm for 7 days.
- 20 Growth of <u>Arthrobacter petroleophagus</u> ATCC 21494 and <u>Brevibacterium</u>

 paraffinolyticum ATCC 21195 was also performed on glucose. Each microorganism was inoculated into 200 ml medium (I) containing 0.2% w/v yeast extract and 2.2% w/v glucose. Growth was performed at 28°C on a rotary shaker at 150 rpm for 24-48 hours.

25



All bacteria were harvested from liquid medium by centrifuging at 8,000 rpm and 4°C for 20 minutes. Cells were washed by resuspending in 50 mM sodium phosphate buffer, pH 7.6 followed by centrifuging as above.

5 Biooxidation Reactions

Biotransformations were performed for each microorganism in 50mM sodium phosphate buffer, pH 7.6 with 5-10 g/l dry cell weight and a substrate concentration of 1 g/l. The cells were incubated with the compound of formula (Ia) on a rotary shaker at 28°C for 18-20 hours.

Samples were removed from the biotransformation and either centrifuged or filtered to remove biomass and analysed directly.

15 Detection of Products

10

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The biooxidation of the compound of formula (Ia) was followed by reverse phase HPLC on a Spherisorb S5-ODS2 reverse phase column eluted with a 50:50 mixture of acetonitrile and 25mM sodium phosphate buffer, pH 7.6 at a flow rate of 0.8 ml/min. Under such conditions the compounds of formulae (IIa) and (Ia) were well resolved with retention times of 5.2 and 9.8 minutes respectively. Both compounds were detected at a wavelength of 300 nm.

The enantiomeric composition of the compound of formula (IIa) formed was investigated by the following method. After removal of biomass the aqueous media was extracted with two volumes of ammonia saturated dichloromethane. The pooled organic extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to afford a pale brown solid. Then the enantiomeric composition of sulfoxide was determined by chiral HPLC on a

30 Chiralpak AD Column under the following conditions:



Column

Chiralpack AD 250 mm x 4.6 mm interior

diameter with 50 mm guard column

5 Eluent

Hexane:Ethanol:Methanol (40:55:5% V/V)

Flow

1.0 ml/min

Injection Volume

20µl

Wavelength

300 nm

Retention times

10 Compound of formula (Ia) 5.1 min

Compound of formula (IIa):

(+) Enantiomer

8.5 min

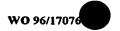
(-) Enantiomer

13.4 min

15 The following results were obtained:

TABLE 2

Microorganism	Compound of Formula (IIa) (ppm)	Enantiomeric excess (%)	Enantiomer ((+) or (-))
Penicitlium frequentans BPFC 386	23	>99	(-)
Penicillium frequentans BPFC 585	2.1	>99	(-)
Penicillium frequentans BPFC 623	3.0	95	(-)
Penicillium frequentans BPFC 733	2.6	87	(-)
Rhizopus stolonifer BPFC 1581	3.0	56	(-)
Ustilago maydis BPFC 1198	8.0	88	(-)
Ustilago maydis BPFC 6333	34.0	99	(-)
Arthrobacter petroleophagus ATCC 21494	24.0	96	(-)
Brevibacterium paraffinolyticum ATCC 21195	13.0	>99	(-)
Acinetobacter sp NCIMB 9871	0.4	17	(-)
Mycobacterium sp BPCC 1174	10.0	97	(-)
Mycobacterium sp BPCC 1178	3.3	93	(+)
Mycobacterium sp BPCC 1179	9.0	96	(-)
Mycobacterium sp BPCC 1186	11.0	97	(-)
Mycobacterium sp BPCC 1187	6.0	96	(-)



The enantiomeric excess value gives an indication of the relative amounts of each enantiomer obtained. The value is the difference between the relative percentages for the two enantiomers. Thus, for example, when the percentage of the (-) enantiomer of the formed sulfoxide is 97.5% and the percentage for the (+) enantiomer is 2.5%, the enantiomeric excess for the (-) enantiomer is 95%.

With <u>Arthrobacter petroleophagus</u> ATCC 21494 and <u>Brevibacterium</u>

paraffinolyticum ATCC 21195 the stereoselectivity of the biooxidation was unaffected by the choice of carbon source used for growth (octane and glucose).

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EXAMPLE 2

Compounds of formula (Id) and (Ie) were screened against a range of microorganisms for the production of the corresponding sulfoxides. The growth of microorganisms and subsequent biotransformations were performed as in Example 1 except that the reaction times were as listed in Tables 5 and 6.

Aspergillus niger BPFC 32 was grown in the same way as the fungi were grown in Example 1.

20 Detection of Products

The biooxidation of the compounds of formula (Id) and (Ie) was followed by reverse phase HPLC as in Example 1 except that the retention times were as follows:

25



TABLE 3

Retention time (min)
13.7
5.0
9.4
4.3

The enantiomeric composition of the compounds of formula (IId) and (IIe) was investigated by the method of Example 1 except in the chiral HPLC the solvent compositions, flow rates and retention times were as follows:

TABLE 4

5

Compound of formula	Solvent Composition	Flow rate (ml/min)	Retention Time
lid	Hexane/Ethanol (70:30% v/v)	1.0	12.9 (Enantiomer A) 21.7 (Enantiomer B)
	Hexane/Ethanol/Methanol (40:55:5% v/v)	1.0	7.4 (Enantiomer A) 10.6 (Enantiomer B)
lle	Hexane/Ethanol (70:30% v/v)	1.0	26.0 (Enantiomer A) 30.5 (Enantiomer B)

In Table 4 the first enantiomer eluted is referred to as enantiomer A and second as enantiomer B. The results are summarised in Tables 5 and 6.



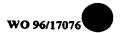




TABLE 5

Microorganism	Reaction time (h)	Aqueous concentration (PPM)		E.e. %	Enantiomer
		Compound of formula (ld)	Compound of formula (lid)		
Mycobacterium sp. BPCC 1174	42	5	16.7	>99	A
Mycobacterium sp. BPCC 1178	42	5.9	14.4	>99	A .
Mycobacterium sp. BPCC 1179	42	6.6	17.4	>99	A
Mycobacterium sp.BPCC 1186	42	4.8	42	>99	
Mycobacterium sp.BPCC 1187	42	7.4	18.3	>99	A
Arthrobacter petroleophagus ATCC 21494	42	3.5	6.6	>99	A
Brevibacterium paraffinolyticum ATCC 21195	42	2.6	21.7	>99	A .
Ustilago maydis BPFC 1198	18	6.7	45	>99	A
Ustilago maydis BPFC 6333	18	4.6	43	>99	A
Aspergilius niger BPFC 32	42	5.6	2.7	-	
Penicillium frequentans BPFC 386	18	5	0	-	
Penicillium frequentans BPFC 585	48	5.2	0	-	•
Penicilium frequentans BPFC 623	48	4.5	0	-	
Penicilium frequentans BPFC 733	18	3.5	0	•	•

(E.e. means Enantiomeric excess)

5 TABLE 6

Microorganism	Reactionti me (h)	Aqueous con- centration (PPM)		E.e (%)	Enant- iorner
		Compound of formula (ie)	Compound of formula (ile)		
Mycobacterium sp. BPCC 1179	42	1.6	3.3	>99	Α
Arthrobacter petroleophagus ATCC 21494	42	3.2	0	-	
Brevibacterium paraffinolyticum ATCC 21195	72	4.0	1.6	-	
Ustilago maydis BPFC 1198	18	2.3	0	-	
Ustilago maydis BPFC 6333	72	3.2	0	-	
Asergillus niger BPFC 32	72	3.7	9.2	-	
Penicitium frequentans BPFC 386	72	3.1	0.5		
Penicilium frequentans BPFC 585	48	3.2	3.2		
Penicitium frequentans BPFC 623	48	2.9	1.5	83.4-	В
Penicillium frequentans BPFC 733	18	3.2	0		-



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The oxidation of the compound of formula (Id) produced in all cases the "A" enantiomer of the compound of formula (IId) in excellent enantiomeric excess but in low yield. The four strains of <u>Penicillium frequentans</u>, previously shown to oxidise the compound of formula (Ia), failed to oxidise the compound of formula (Id).

The oxidation of the compound of formula (Ie) produced fewer results. This compound proved to be particularly insoluble making the detection of product difficult. Whilst in a number of cases sulfoxide was produced, its concentration was too low to determine the enantiomeric excess. However two results were obtained with Mycobacterium sp. and Penicillium frequentans both affording sulfoxide of high enantiomeric excess but interestingly of opposite stereoselectivity.

15 EXAMPLE 3

The microorganisms listed in Table 9 below were screened for sulfoxidation activity against compounds of formula (Ib). They were grown under the same condition as in Examples 1 and 2.

20

Biotransformations were performed following the protocol of Example 1 except that the dry cell weight was increased to approximately 20gL⁻¹ and the reaction time was extended.

25 Detection of Products

The biooxidation of the compound of formula (Ib) was followed by reverse phase HPLC as in Example 1 except that the retention times were as follows:

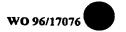


TABLE 7

Compound of formula	Retention time (min)
Ib	8.1
IIb	4.2

The enantiomeric composition of the compound of formula (IIb) was investigated by the method of Example 1 except in the chiral HPLC the solvent composition,

flow rate and retention time were as follows:

TABLE 8

Solvent composition	Flow Rate (ml/min)	Retention times (min)
Hexane/ethanol (70:30%)	1.0	32.3 (Enantiomer A) 36.6 (Enantiomer B)

In Table 8 the first enantiomer eluted is referred to as enantiomer A and the second as enantiomer B.

The results are summarised in the following table:

TABLE 9

Microorganism	Reaction time (h)	Aqueous concentration (PPM)		E.e (%)	Enantio- mer
		Compound of formula (lb)	Compoun d of formula (ilb)		
Mycobacterium sp. BPCC 1178	72	8.6	3.4	8.2	В
Brevibacterium paraffinolyticum ATCC 21195	72	8.4	4.0	26.6	В
Ustilago maydis BPFC 6333	72	8.2	4.3	>99	A
Aspergillus niger BPFC 32	72	5.6	28.0	>99	A
Penicillium frequentans BPFC 386	72	8.4	4.5		
Penicilium frequentans BPFC 585	48	6.5	11.4	۱.	
Penicilium frequentans BPFC 623	48	7.7	6.5		•



(E.e. means enantiomeric excess)

The microorganisms listed in Table 9 were also screened under identical conditions for sulfoxidation of the compound of formula (Ic) but no product of formula (IIc) could be detected.

Deposits Of Microorganisms

- The following microorganisms were deposited at the National Collections of Industrial and Marine Bacteria Ltd (NCIMB), 23 St. Machar Drive, Aberdeen, Scotland AB2 1RY on 25 November 1994:
 - Mycobacterium sp BPCC 1174
- 15 Accession No. NCIMB 40695
 - 2. <u>Mycobacterium</u> sp BPCC 1178

Accession No. NCIMB 40696

- 3. Mycobacterium sp BPCC 1179
 - Accession No. NCIMB 40697
- 20 4. Mycobacterium sp BPCC 1186

Accession No. NCIMB 40698

5. Mycobacterium sp BPCC 1187

Accession No. NCIMB 40699

The following microorganisms were deposited at the International

- 25 Mycological Institute (IMI), Bakeham Lane, Englefield Green, Egham, Surrey TW20 9TY, England on 28 November 1994:
 - 6. Penicillium frequentans BPFC 386

Accession No. IMICC 364802

- 7. Penicillium frequentans BPFC 585
- 30 Accession No. IMICC 364801
 - 8. Penicillium frequentans BPFC 623



Accession No. IMICC 364800

- Penicillium frequentans BPFC 733
 Accession No. IMICC 364799
- 10. Rhizopus stolonifer BPFC 1581
- 5 Accession No. IMICC 364798
 - 11. <u>Ustilago maydis</u> BPFC 1198 Accession No. IMICC 364797
 - 12. <u>Ustilago maydis</u> BPFC 6333 Accession No. IMICC 364796
- 10 13. <u>Asperigillus niger</u> BPFC 32Accession No. IMICC 364795



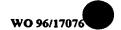


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(PCT Rule 13bis)

A. The indications made below relate to the m	iczoczani	sm referred to in the description		
on page 20	, line	15		
B. IDENTIFICATION OF DEPOSIT		Further deposits are identified on an additional sheet		
Name of depositary institution				
The National Collections	of Ir	ndustrial and Marine Bacteria Limited		
Address of depositary institution (including posts 23 St Machar Drive ABERDEEN AB2 1RY	code and c	country)		
Scotland, United Kingdom				
Date of deposit	·	Accession Number		
November 25, 1994		NCIMB 40695		
C. ADDITIONAL INDICATIONS (leave b)	lenk if not ep	oplicable) This information is continued on an additional sheet		
In respect of all designated states in which such action is possible and to the extent that it is legally permissible under the law of the designated state, it is requested that a sample of the deposited micro-organism(s) be made available only by the issue thereof to an independent expert, in accordance with the relevant patent legislation, e.g. EPC Rule 28(4), U.K. Rule 17(3), Australian Regulation 3.25(3) and generally similar provisions mutatis mutandis for any other designated state.				
D. DESIGNATED STATES FOR WHICH	INDIC/	ATIONS ARE MADE (if the indications are not for all designated States)		
E. SEPARATE FURNISHING OF INDIC				
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B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution	
The National Collections of Industrial	and Marine Bacteria Limited
Address of depositary institution (including postal code and cour	P(7))
23 St Machar Drive	
ABERDEEN AB2 1RY	
Scotland, United Kingdom	
Date of deposit November 25, 1994	Accession Number
November 25, 1994	NCIMB 40696
C. ADDITIONAL INDICATIONS (leave blank if not applications)	cable) This information is continued on an additional sheet
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A. The indications made below relate to the microorganism referred to in the description on page 20 , line 19	
B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution	
The National Collections of Industrial a	nd Marine Bacteria Limited
Address of depositary institution (including postal code and country)
23 St Machar Drive ABERDEEN AB2 1RY Scotland, United Kingdom	
Date of deposit	Accession Number
November 25, 1994	NCIMB 40697
C. ADDITIONAL INDICATIONS (loave blank if not applicable	(k) This information is continued on an additional about
In respect of all designated states in what the extent that it is legally permissible it is requested that a sample of the deposit available only by the issue thereof to an with the relevant patent legislation, e.g. Australian Regulation 3.25(3) and general mutandis for any other designated state.	e under the law of the designated state, osited micro-organism(s) be made in independent expert, in accordance g. EPC Rule 28(4), U.K. Rule 17(3), ally similar provisions mutatis
D. DESIGNATED STATES FOR WHICH INDICATIO	NS ARE MADE (if the indications are not for all designated States)
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(PCT Rule 136is)

A. The indications made below relate to the microorganism referred to in the description				
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В.	IDENTIFIC	ATION OF DEPOSIT		Further deposits are identified on an additional abeet
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The	National	Collections of Indu	strial an	nd Marine Bacteria Limited
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	e of deposit rember 25,	1994		Accession Number NCIMB 4069B
C.	ADDITIONA	L INDICATIONS (leave blenk	if not epplicable	(c) This information is continued on an additional sheet
In respect of all designated states in which such action is possible and to the extent that it is legally permissible under the law of the designated state, it is requested that a sample of the deposited micro-organism(s) be made available only by the issue thereof to an independent expert, in accordance with the relevant patent legislation, e.g. EPC Rule 28(4), U.K. Rule 17(3), Australian Regulation 3.25(3) and generally similar provisions mutatis mutandis for any other designated state.				
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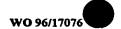


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A. The indications made below relate to the microorganism re on page	
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B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet X
Name of depositary institution	
International Mycological Institute	
Address of depositary institution (including postal code and country Bakeham Lane Egham Surrey TW20 9TY, England, UK	ין
Date of deposit	T
November 28, 1994	Accession Number IMICC 364802
C. ADDITIONAL INDICATIONS (leave blank if not applicable	ble) This information is continued on an additional sheet
In respect of all designated states in we the extent that it is legally permissible it is requested that a sample of the deplet available only by the issue thereof to a with the relevant patent legislation, e. Australian Regulation 3.25(3) and general mutandis for any other designated state. D. DESIGNATED STATES FOR WHICH INDICATION	e under the law of the designated state, osited micro-organism(s) be made in independent expert, in accordance g. EPC Rule 28(4), U.K. Rule 17(3), lly similar provisions mutatis
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A. The indications made below relate to the microorganism re	ferred to in the description
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International Mycological Institute	•
Address of depositary institution (including postel code and country Bakeham Lane Egham Surrey TW20 9TY, England, UK)
Date of deposit	
November 28, 1994	Accession Number IMICC 364801
C. ADDITIONAL INDICATIONS (lowe blank if not applicable	(c) This information is continued on an additional abeet
In respect of all designated states in whithe extent that it is legally permissible it is requested that a sample of the deposavailable only by the issue thereof to an with the relevant patent legislation, e.g. Australian Regulation 3.25(3) and general mutandis for any other designated state. D. DESIGNATED STATES FOR WHICH INDICATION.	e under the law of the designated state, esited micro-organism(s) be made independent expert, in accordance EPC Rule 28(4), U.K. Rule 17(3), ly similar provisions mutatis
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A. The indications made below relate to the microorganism referred to in the description on page 21 , line 1	
B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution	
International Mycological Institute	e
Address of depositary institution (including postal code and	nd country)
Bakeham Lane	
Egham	
Surrey TW2O 9TY, England, UK	
Date of deposit	Accession Number
November 28, 1994	IMICC 364800
C. ADDITIONAL INDICATIONS (leave blank if not	applicable) This information is continued on an additional sheet
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B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution	
International Mycological Institute	e
Address of depositary institution (including postal code an	ul country)
Bakeham Lane	
Egham	
Surrey	
TW20 9TY, England, UK	
Date of deposit	Accession Number
November 28, 1994	Accession Number IMICC 364799
C. ADDITIONAL INDICATIONS (leave blank if not	sepplicable) This information is continued on an additional about
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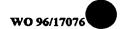


on page 21 , line	ism referred to in the description
B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositary institution	
International Mycological Institute	
Address of depositary institution (including postal code and	country)
Bakeham Lane	
Egham Surrey	
TW20 9TY, England, UK	
Date of deposit	Accession Number
November 28, 1994	IMICC 364798
C. ADDITIONAL INDICATIONS (loave blank if not a	pplicable) This information is continued on an additional sheet
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A. The indications made below relate to the microorganism referred to in the description		
on page 21 , line 7		
B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet	
Name of depositary institution		
International Mycological Institute		
Address of depositary institution (including postal code and country	,	
Bakeham Lane		
Egham Surrey		
TW20 9TY, England, UK		
Date of deposit November 28, 1994	Accession Number	
November 20, 1994	IMICC 364797	
C. ADDITIONAL INDICATIONS (leave blank if not applical		
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available only by the issue thereof to a	on independent expert, in accordance	
with the relevant patent legislation, e.	.a. EPC Rule 28(4). U.K. Rule 17(3)	
Australian Regulation 3.25(3) and general mutandis for any other designated state.	ally similar provisions mutatis	
D. DESIGNATED STATES FOR WHICH INDICATION		
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B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet
Name of depositsry institution International Mycological Institute	
Address of depositsry institution (including postal code and country	r)
Bakeham Lane Egham Surrey TW20 9TY, England, UK	,
Date of deposit	Accession Number
November 28, 1994	IMICC 364796
C. ADDITIONAL INDICATIONS (leave blank if not applical	this information is continued on an additional about
In respect of all designated states in the extent that it is legally permissib it is requested that a sample of the de available only by the issue thereof to with the relevant patent legislation, e Australian Regulation 3.25(3) and general mutandis for any other designated state. D. DESIGNATED STATES FOR WHICH INDICATION.	le under the law of the designated state posited micro-organism(s) be made an independent expert, in accordance .g. EPC Rule 28(4), U.K. Rule 17(3), ally similar provisions mutatis
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A The indications made below to	<u> </u>	
A. The indications made below relate to the microorganism referred to in the description on page 21 , line 11		
B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sheet X	
Name of depositary institution		
International Mycological Institute		
Address of depositary institution (including postal code and country Bakeham Lane Egham Surrey TW20 9TY, England, UK)	
Date of deposit November 28, 1994	Accession Number IMICC 364795	
C. ADDITIONAL INDICATIONS (leave blank if not applicable	(c) This information is continued on an additional sheet	
In respect of all designated states in we the extent that it is legally permissible it is requested that a sample of the deposarilable only by the issue thereof to a with the relevant patent legislation, e. Australian Regulation 3.25(3) and general mutandis for any other designated state. D. DESIGNATED STATES FOR WHICH INDICATION	e under the law of the designated state, osited micro-organism(s) be made n independent expert, in accordance g. EPC Rule 28(4), U.K. Rule 17(3), lly similar provisions mutatis NS ARE MADE (if the indications are not for all designated States)	
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CLAIMS

1. A method of preparing a compound of formula (II) either as a single enantiomer or in an enantiomerically enriched form:

5 wherein:

Het
$$_1$$
 is $\begin{array}{c} R_2 \\ R_3 \\ \end{array}$ or $\begin{array}{c} R_4 \\ R_5 \end{array}$

and

Het
$$_2$$
 is $\stackrel{\mathsf{N}}{\underset{\mathsf{R}_{10}}{\bigvee}} \overset{\mathsf{R}_6}{\underset{\mathsf{R}_9}{\bigvee}}$ or $\overset{\mathsf{N}}{\underset{\mathsf{R}_{10}}{\bigvee}} \overset{\mathsf{S}}{\underset{\mathsf{R}_{10}}{\bigvee}}$

10 and

X is
$$-CH$$
 or R_{13}

wherein:

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_s-R_s optionally may be exchanged for an unsubstituted nitrogen atom;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl, phenylalkoxy;

5 R₄ and R₄ are the same or different and selected from hydrogen, alkyl, aralkyl;

R_s is hydrogen, halogen, trifluoromethyl, alkyl, alkoxy;

R₆ - R₇ are the same or different and selected from hydrogen, alkyl, alkoxy,
10 halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl or
adjacent groups R₆ - R₇ may complete together with the carbon atoms to which
they are attached optionally substituted ring structures;

R₁₀ is hydrogen or alkoxycarbonyloxymethyl;

15

20

 R_{ii} is hydrogen or forms an alkylene chain together with R_{ij}

R₁₂ and R₁₃ are the same or different and selected from hydrogen, halogen or alkyl; which method comprises stereoselective biooxidation of the pro-chiral sulfide counterpart compound.

2. A method according to claim 1 wherein:

25 and

Het $_2$ is $\underset{R_{10}}{\overset{R_6}{\underset{R_9}{\bigvee}}}$

and

5

wherein $R_{_{1}}$, $R_{_{2}}$, $R_{_{3}}$, $R_{_{6}}$ - $R_{_{9}}$, $R_{_{10}}$ and $R_{_{11}}$ are as defined in claim 1.

3. A method to claim 1 or 2 wherein the compound of formula (II) is a

compound of formula:

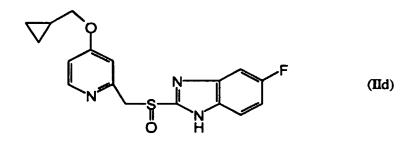
OCH₃

H₃C

CH₃

10





$$H_3C$$
 CH_3
 CH_3
 CH_3
 CH_3

- 5 4. A method according to any one of the previous claims wherein a single enantiomer of the compound of formula (II) is prepared.
 - 5. A method according to claim 3 wherein there is prepared a compound of formula (IIa) and the biooxidation is carried out with a microorganism which is

10

Penicillium frequentans

Brevibacterium paraffinolyticum or

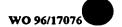
Mycobacterium sp.

15 6. A method according to claim 3 wherein there is prepared a compound of formula (IIb) and the biooxidation is carried out with a microorganism which is:

Aspergillus niger or

Ustilago maydis.

20



7. A method according to claim 3 wherein there is prepared a compound of formula (IId) and the biooxidation is carried out with a microorganism which is

Mycobacterium sp.

- 5 <u>Arthrobacter petroleophagus</u>
 Brevibacterium paraffinolyticum or
 Ustilago maydis.
- 8. A method according to claim 3 wherein there is prepared a compound of formula (IIe) and the bioxidation is carried out with a microorganism which is:

Mycobacterium sp.

Penicillium frequentans

- 9. A method according to claim 1 substantially as described in any one of the Examples.
- 10. A compound of formula II, as a single enantiomer or in enantiomerically enriched form, as defined in claim 1 prepared by the method claimed in any one20 of claims 1 to 9.

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C12P 11/00, C07D 401/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, IFIPAT, CA, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0005129 A1 (AB HÄSSLE), 31 October 1979 (31.10.79)	1-4
		
A	Chem. Rev., Volume 88, 1988, H.L. Holland, "Chiral Sulfoxidation by Biotransformation of Organic Sulfides" page 473 - page 485	1-10
		
A	Drug Metabolism and Disposition, Volume 21, No 4, 1993, J.R. Cashman et al., "Chemical, Enzymatic and Human Enantioselective S-Oxygenation of Cimetidine" page 587 - page 597	1-10
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1	N.	Former documents are listed in the continuation of Box C.		See patent family annex.
	•	Special categories of cited documents:	Т-	later document published after the international filing date or pri-
I	*A*	document defining the general state of the art which is not considered to be of particular relevance		date and not in conflict with the application but cited to understa the principle or theory underlying the invention

"E" ertier document but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other

special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other

document published prior to the international filing date but later than the priority date claimed

riority

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report		
19 March 1996	2 1 -03- 1996		
Name and mailing address of the ISA/	Authorized officer		
Swedish Patent Office Box 5055, S-102 42 STOCKHOLM	Gerd Strandell		
Facsimile No. +46 8 666 02 86	Telephone No. +46 8 782 25 00		

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International application No. PCT/SE 95/01415

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No	
A	Enzyme Microb. Technol., Volume 3, 1981, R.S. Philips, S.W. May, "Enzymatic sulphur oxygenation reactions" page 9 - page 18		
			
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INTERMITIONAL SEARCH REPORT

Information on patent family members

ite...ational application No.

05/02/96 PCT/SE 95/01415

Patent of cited in se	document arch report	Publication date	Patent family member(s)		Publication date
EP-A1- 0005129 31/	31/10/79	31/10/79 SE-T3-	0005129		
			AT-B-	374471	25/04/84
			AT-B-	374472	25/04/84
			AT-B-	374473	25/04/84
			AT-B-	375365	25/07/84
			AT-B-	389995	26/02/90
			AU-B.B-	529654	16/06/83
			AU-A-	4602779	18/10/79
•			CA-A-	1127158	06/07/82
			CA-A-	1129417	10/08/82
			JP-C-	1312930	28/04/86
			JP-C-	1504537	13/07/89
			JP-A-	54141783	05/11/79
			JP-A-	58192880	10/11/83
			JP-B-	60034956	12/08/85
			JP-B-	63053191	21/10/88
			LU-A-	88307	04/05/94
			SE-A-	7804231	15/10/79
			SU-A,A-	89529 <i>2</i>	30/12/81
			US-A-	4255431	10/03/81
			US-A-	4337257	29/06/82
			US-A-	4508905	02/04/85

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